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Research Article

Study of Maternal and Fetal Doppler Velocimetry, Histopathology of Placental Bed in Diabetic Pregnancy and Its Correlation to Fetal Outcome

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Abstract:

Diabetes mellitus still represents an important medical problem during pregnancy, causing perinatal morbidity and mortality. Despite improved outcome reflected by a steep decline in perinatal mortality over the past few decades, controversy still exists regarding the care of the pregnant woman with both pre-existing and gestational Diabetes Mellitus. Doppler ultrasound is especially valuable during pregnancy because fetal maternal and placental circulations can be studied.

The aim of this work was to study the vascular changes in the uteroplacental and fetoplacental circulations, and to correlate these findings with histopathology of the placenta and placental bed, which may occur in association with diabetic pregnancies. The study was carried out on 100 pregnant women of comparable age and parity. They were divided into 2 groups. The control group comprising 20 normal non-diabetic pregnant women and the normotensive diabetic group comprising 80 pregnant diabetic women. All were singleton pregnancies of 34 weeks or more and were delivered by C.S the control and the study cases were subjected to history taking and thorough physical examination. They were also subjected to ultrasonographic examination for fetal biometric parameters and for Doppler examination. Doppler examination included umbilical artery, uterine arteries fetal middle cerebral artery. At the time of C.S the placenta and placental bed biopsy was obtained. After delivery, the Apgar score of the newborn was assessed at 1 and 5 minutes, the body weight was measured, and the fetus was followed up for any complications.

Result: There was a positive correlation between the umbilical artery PI and the mean blood glucose levels indicating that poor diabetic control is probably associated with increased umbilical artery PI. However, there was no significant difference between the mean value of the umbilical artery PI in the diabetic and control groups. The uterine arteries Doppler indices showed no significant findings between the diabetic and the control groups. Neither did the uterine arteries Doppler indices show a correlation with the mean blood glucose levels. There was no significant difference between the middle cerebral artery PI in the diabetic and control groups. This observation indicates that there was no redistribution in the fetal circulation in the fetuses of the diabetic group. There was also non correlation between the MCA Doppler indices and the glycemic control. Histopathologic studies of the placental bed showed marked difference between the diabetic group and the control group as regards lack of physiologic changes and arteriosclerotic changes, which emphasizes the effect of diabetes on the placental bed vasculature.

Conclusion: Abnormal umbilical artery waveform analysis is one of significant predictors of fetal compromise in diabetic pregnancy, but fetal compromise can occur in association with normal Doppler waveform analysis. In maternal diabetes the classic redistribution seen in fetal hypoxemia due to uteroplacental insufficiency may not occur in diabetic patient even in severely compromised fetuses. In maternal diabetes mellitus, maternal glycemic control has no effect on impedance to flow in the uterine and middle cerebral arteries. No relationship was found between the uterine or umbilical arteries Doppler indices and the placental bed decidual vascular pathology in diabetic pregnancies. There was no correlation between placental findings and the Doppler waveform analysis of the umbilical and the uterine arteries.

Key words: fetal doppler velocimetry; diabetic pregnancy; fetal outcome

Introduction

Diabetes mellitus is a common medical condition sometimes complicating pregnant women. It is estimated that 1 out of every 200 pregnancies is complicated by progestational diabetes mellitus and additionally, that 5 in every 200 pregnant women will develop gestational diabetes **[1].**

Diabetic pregnancy is associated with increased perinatal morbidity and mortality due to congenital malformations, 'unexplained' intra – uterine fetal death and fetal macrosomia **[2].**

A recent method for antenatal fetal health assessment is the Doppler ultrasound which is used for hemodynamic assessment of maternal and fetal circulations **[3]**.

Doppler ultrasound is a noninvasive method of studying the flow velocity within blood vessels, and especially valuable during pregnancy because fetal, maternal, and placental circulations can be studied **[4].**

The placenta of the diabetic women has attracted much interest because placental dysfunction is postulated as being partially responsible for the unduly high frequency of perinatal complications **[5].**

A great interest in studying uteroplacental vasculature has developed, as their lesions may be involved in the pathogenesis of placental insufficiency in pregnancies complicated by hypertension and diabetes **[6].**

Aim of the work:

The aim of this work is to study vascular changes in fetal and placental circulations using ultrasound Doppler velocimetry and correlate it with placental and placental bed histopathological findings in diabetic pregnant females.

Patients and methods:

This study was carried out on 100 pregnant women admitted in the Obstetrics and Gynecology Department of Al Azhar University Hospitals, during the period from April 2019 to November 2020.

Case's Selection

The patients were grouped into two groups as follow:

The Control Group (Normal Pregnancy):

This group consisted of 20 nondiabetic pregnant women.

Inclusion criteria

- Singleton pregnancy.
- Gestational age ≥ 34 weeks.
- No obstetric complications.
- No medical disorders.
- Expected to be delivered by cesarean section (C.S) for example (contracted pelvis, previous 2 C.S).

The study group (diabetic pregnancy):

This group consisted of 80 diagnosed diabetic pregnant women, all types of diabetes were included, diabetic patients with type I, II and gestational diabetes.

Inclusion Criteria

- Singleton pregnancy.
- No congenital anomalies
- No history of chronic medical disease other than diabetes.
- All cases were expected to be delivered by C.S. For example (contracted pelvis, previous 2C.S).
- Gestational age ≥ 34 weeks.

All the patients in the study were subjected to the following:

Full history taking.

General and obstetric examinations.

Laboratory investigations:

Fasting and 2 hours postprandial blood glucose level, and mean blood glucose level estimated. Other investigations for antenatal care.

Sonographic examination:

The patients were subject to sonographic obstetric examination using Toshiba SSA 270 A for:

a) Fetal Biometry Biparietal diameter, femur length, abdominal circumference, and fetal weight.

b) Placental site and grading.

c) Amniotic fluid volume and aspect.

d) Assessment of any fetal anomalies.

Doppler Study:

Pulsed wave Doppler studies were performed on uterine, umbilical and middle cerebral arteries, the size of the sample volume was adapted to the vessel diameter to cover it entirely. All recordings used for measurements of fetal circulation were obtained in the absence of fetal body and breathing movements and at fetal heart rate of 120-160 beats/minute. The angle between the ultrasound beam and the direction of the flow in the vessels was always less than50˚.

All Doppler measurements were taken with 3 consecutive well-defined waveforms.

The UTERINE ARTERY DOPPLER (RIGHTAND LEFT UTERINE ARTERIES) e following vessels were studied:

The uterine velocity waveforms were obtained either vaginally or abdominally.

For vaginal studies:

Patient in supine position with her thighs abducted and knee flexed. The transducer (vaginal probe 7.5MHz) was placed into a sterile glove with coupling jelly and then introduced into the lateral vaginal fornix

For abdominal studies:

The abdominal studies were carried by placing the transducer (3.5 MHz) on the anterior abdominal wall in the right and left lower quadrants aimed into the lower uterine segment and gently moved around until the appropriate velocity waveforms are seen.

The main uterine artery was the target of study and the resistance index was the chosen measurement for analysis.

Fetoplacental Circulation: (Fetal Umbilical Artery)

The fetal umbilical artery was selected as a measurement for the fetal perfusion and blood supply of the fetal side of the placenta. It is measured

by selecting one umbilical artery from a free loop of the umbilical cord **[7].**

The pulsatility index of the umbilical artery was the chosen measurement for the analysis.

Fetal Middle Cerebral Artery

The standard plane was first obtained to measure the biparietal diameter. This plane included the thalamus and cavum of the septum pellucidum. Pulsations or flow of the middle cerebral artery could be seen at the level of the insula. The sample volume was placed over the middle cerebral artery and maximum flow velocity waveforms were recorded (**8**).

Histopathologic Studies

Placental Bed Biopsy

Placental bed biopsy was obtained at the time of Cesarean section under direct visualization of the placental site. The technique used was originally described by **Robertson et al. (2016) [9].** After delivery of the baby, the site of the placenta was identified, and then the placenta was peeled away from its bed by the surgeon, while the site of the placenta was marked by the assistant by keeping a finger on the serosal surface opposite to the area specified. After delivery of the placenta, its site is checked by being somewhat depressed, focally disrupted and friable when compared with the smooth but undulating surrounding decidua parietals. This site was inspected for bleeding vessels, and a biopsy was taken using an ovum forceps or curved scissors. The biopsy was approximately one cm in diameter and half cm in depth including bleeding vessels whenever possible. A single hemostatic suture was inserted when needed. No problems were encountered with technique except that it was more difficult to perform when the placenta was anteriorly situated, but if the uterus was partially exteriorized and the upper lip of the lower segment incision is everted by the assistant, adequate access to the anterior placental site can be achieved.

The biopsy was fixed in formalin by placing it in 4% buffered neutral formaldehyde saline solution (the so called 10% formal saline). After 12 to 24 hours of primary fixation, the biopsy specimen can be cut into strips of about 3mm breadth, each strip being properly oriented in the ultimate wax block to yield perpendicular sections from the decidual surface to the myometrial base.

Conventional histopathological methods were used, and the paraffin sections stained with

1- Hematoxylin and Eosin.
2- Periodic acid Schiff technique (PAS)
3- Verhoff Van Geison satin were used to study the spiral arteries

All the biopsies were examined histopathologically for:

1. Lack of physiologic changes.
2. Blood thrombi.
3. Interstitial hemorrhage.
4. Fibrinoid necrosis.
5. Elastosis and hyalinosis (Verhoff Van Geison)
6. Atherosis (Verhoff Van Geison)
7. Intimal thickening. (PAS)
8. Exaggerated cytotrophoblastic mitosis.
9. Endarteritis.

According to the degree of pathology, the diabetic group was further subdivided into: (Barth et al., 2017) (10).

- Group I: normal decidual vasculature.
- Group II: patients with blood thrombi, fibrinoid necrosis, atherosis or thickening.
- Group III: patients with blood thrombi, fibriniod necrosis, atherosis or endarteritis.

Placental biopsy:

Each placenta with the cord and membranes was immersed in 10% formaline and left several days for fixation. This allows for easier handling and cutting of the placenta. Coronal sections being cut 1cm intervals and tissue samples were taken from a macroscopically normal central portion of the placenta avoiding the first 2cm form the margin **[11].** This procedure was carried out without attempting to perform gross examination. Section of paraffin embedded tissues were stained with

1- Haematoxylin and Eosin,

2- PAS and Verhoff Van Geison stain.

All sections were examined by the same pathologist without knowledge of the clinical history and blood flow results.

All the biopsies are examined histopathologically for:

1. Lack of physiologic changes.
2. Fibrin thrombi.
3. Blood thrombi.
4. Interstitial hemorrhage.
5. Fibrinoid necrosis.
6. Elastosis and hyalinosis (Verhoff Van Geison).
7. Atherosis (Verhoff Van Grison).
8. Intimal thickening. (PAS).
9. Calcification.
10. Infarcts.
11. Endarteritis.
12. Interstitial oedema.
13. Thickening of the villous membrane.

Assessment of the fetal outcome:

1. Apgar score at one and five minutes.
2. Careful examination for any evidence of congenital anomalies.
3. Assessment of the fetal birth weight.

Statistical Analysis

All statistics were performed on an IBM compatible PC with Microsoft Excel spread sheet package version 9.0.

Results:

There was a significant increase of blood glucose (fasting, 2h-pp and the mean) in the diabetic group compared to the control one, with no significant difference between them in the age and parity. No significant variation is detected regarding umbilical artery PI in both groups. No significant variation between rights, left and mean uterine arteries RI in both groups of the study (table 1, 2, 3).

	Control group (No = 20)		Diabetic group (No= 80)		t	P
	Range	X ± SD	Range	X ± SD		

Table (1): *Clinical data of the control and study groups*

umbilical artery (PI)	Control (No=20)	Diabetic (No=80)	T	P
Range	0.78- 1.35	0.75 – 3.67	0.324	> 0.05
Mean ± SD	0.98 ± 0.18	1.16 ± 0.58		

Table (2): *Comparison between the control and diabetic groups as regards the umbilical artery pulsatility index*

uterine arteries (RI)		Range	Mean ± SD	T	P
Right	Control (20)	0.36- 0.59	0.49 ± 0.08	0.133	>0.05
	Diabetic (80)	0.31-0.78	0.48 ± 0.11		
Left	Control (20)	0.32-0.76	0.54 ± 0.12	1.06	>0.05
	Diabetic (80)	0.21-0.69	0.49 ± 0.11		
Mean	Control (No=20)	0. 43-0.63	0.51 ± 0.07	1.76	> 0.05
	Diabetic (No=80)	0.28- 0.78	0.48 ± 0.1		

Table (3): *Comparison between the control and the diabetic groups as regards the right, left, and mean uterine arteries resistance index*

No significant difference in cerebroumbilical ratio between the control and the diabetic groups. No significant variation as regards middle cerebral artery PI, in both groups of the study (table 4).

the middle cerebral artery (PI)	Range	Mean ± SD	T	P
Control No. (20)	1.07- 2.5	1.85 ±0.54	0.264	> 0.05
Diabetic No. (80)	1.11-2.68	1.92 ± 0.47		
the cerebro /umbilical ratio	**Range**	**Mean ± SD**	**T**	**P**
Control No. (20)	1.0-3.28	1.98 ± 0.85	0.275	> 0.05
Diabetic No. (80)	0.63-2.94	1.82 ± 62		

Table (4): *Comparison between the control and diabetic groups as regards the middle cerebral artery Pulsatility index and the cerebro /umbilical ratio*

The umbilical artery PI showed significant positive correlation with mean blood glucose. Neither the uterine arteries RI nor the middle cerebral artery PI showed significant correlation with mean blood glucose level in diabetic group (table 5).

the mean blood glucose level.	Correlation coefficient	P- value
Umbilical PI	0.48	< 0.05
Right uterine RI	0.13	> 0.05
Left uterine RI	0.30	> 0.05
Mean uterine RI	0.21	> 0.05
MCA PI	0.19	> 0.05

Table (5): *The correlation between Doppler parameters and the mean blood glucose level.*

There was significant difference between control and diabetic groups as regards histopathological changes of placental bed as lack of physiologic changes, blood thrombi, interstitial hemorrhage, fibrinoid necrosis, hyalinosis and mural thickening focal atherosis, intimal thickening, endarteritis, exaggerated cytotrophoblastic mitosis.No significant difference between both groups as regards lack of physiologic changes, but there is high significant elevation of different placental changes in diabetic group as thrombi (fibrin & blood), interstitial hemorrhage, fibrinoid necrosis, atherosis intimal thickening and interstitial oedema, also there is significant increase of hyalinosis ad mural thickening, calcification , infarcts, endarteritis and thickening of villous membrane (table 6).

placental bed biopsy	Control (No=20)	Diabetic (No=80)	χ^2	P
Lack of physiologic changes	2 (10 %)	25 (31 %)	3.6	< 0.05
Blood thrombi	-	14 (18 %)	4.04	< 0.05
Interstitial hemorrhage	-	16 (20 %)	4.7	< 0.05

Fibrinoid necrosis	-	14 (18 %)	4.04	< 0.05
Hyalinosis and mural thickening	-	26 (33 %)	8.7	< 0.01
Focal atherosis	-	14 (18 %)	4.04	< 0.05
Intimal thickening	-	15 (19 %)	4.4	< 0.05
Endarteritis	-	14 (18 %)	4.04	<0.05
Exaggerated cytotrophoblastic mitosis	-	14 (18 %)	4.04	< 0.05
placental biopsy	**Control (No= 20)**	**Diabetic (No=80)**	χ^2	**P**
Lack of physiologic changes	2 (10%)	8 (10 %)	0.02	> 0.05
Fibrin thrombi	2 (10%)	32(40%)	6.7	< 0.01
Blood thrombi	-	22 (27%)	7.05	< 0.01
Interstitial hemorrhage	-	25 (31%)	8.3	< 0.01
Fibrinoid necrosis	-	37 (47%)	14.86	< 0.01
Hyalinosis and mural thickening	1 (5 %)	26 (33%)	5.15	< 0.05
Focal atherosis	-	22 (27%)	7.05	< 0.01
Intimal thickening	-	26 (33%)	8.7	< 0.01
Calcification	1 (5%)	20 (25%)	3.8	< 0.05
Infarcts	-	12 (15 %)	4.4	< 0.05
End arteritis	-	12 (15%)	4.4	< 0.05
Interstitial oedema	2 (10 %)	32 (40%)	6.7	< 0.01
Thickening of villous membrane	-	14 (18%)	4.4	< 0.05

Table (6): *Comparison between the control and diabetic groups as regards the histopathologic criteria of placental bed and the placental biopsy.*

In diabetic patients there was no significant difference between cases with positive and cases with negative lack of physiological changes in placental bed as regards mean blood glucose, umbilical PI, mean uterine RI, C/U ratio, fetal birth weight and Apgar score. In diabetic patients there was no significant difference between cases with positive and cases with negative fibrin thrombi in placental biopsy as regards mean blood glucose, umbilical artery PI, mean uterine artery RI, fetal birth weight and Apgar score at 5 min**.** In diabetic patients there was no significant difference between cases with positive and cases with negative blood thrombi in placental biopsy as regards mean blood glucose, umbilical artery PI, mean uterine artery RI, fetal birth weight and Apgar score at 5 min**.** In diabetic patients there was no significant difference between cases with positive and cases with negative interstitial hemorrhage in placental biopsy as regards mean blood glucose, umbilical artery PI, mean uterine artery RI, fetal birth weight and Apgar score at 5 min**.** In diabetic patients there was no significant difference between cases with positive and cases with negative fibrinoid necrosis in placental biopsy as regards mean blood glucose, umbilical artery PI , mean uterine artery RI, and Apgar Score at 5 min but fetal birth weight showed significant difference .In diabetic patients there was no significant difference between cases with positive and cases with negative hyalinosis and mural thickening in placental biopsy as regards mean blood glucose, umbilical artery PI, mean uterine artery RI, fetal birth weight and Apgar score 5 min**.** In diabetic patients there was no significant difference between cases with positive and cases with negative focal atherosis in placental biopsy as regards mean blood glucose, umbilical artery PI, mean uterine artery RI, fetal birth weight and Apgar score at 5 min**.** In diabetic patients there was no significant difference between cases with positive and cases with negative Intimal thickening in placental biopsy as regards mean blood glucose, umbilical artery PI, mean uterine artery RI, and Apgar score at 5 min but fetal birth weight showed significant difference .In diabetic patients there was no significant difference between cases with positive and cases with negative interstitial oedema in placental biopsy as regards mean blood glucose, umbilical artery PI, mean uterine artery RI, fetal birth weight and Apgar Score 5 min (table 7).

lack of physiological changes in placental bed	**Positive (25)**	**Negative (55)**	**P- value**
Mean Blood glucose	133 (± 11.22)	124.11(± 23.52)	> 0.05
Umbilical PI	1.19 (± 0.28)	1.17 (± 0.64)	> 0.05
Mean uterine RI	0.47 (± 0.06)	0.50 (±0.11)	> 0.05
C/U Ratio	2.04 (± 0.56)	1.78 (± 0.63)	> 0.05
Fetal Birth weight	3582 (±376.83)	4012.11(± 746.67)	> 0.05
Apgar Score	7.61 (± 0.89)	7.57 (±0.78)	> 0.05
placental fibrin thrombi in placental biopsy	Positive (32)	Negative (48)	P – value
Mean blood glucose	130.5 ±18.77	125.11 ± 23.28	P > 0.05
Umbilical PI	1.33 ± 0.89	1.07 ± 0.22	P > 0.05
Mean uterine RI	0.46 ± 0.11	0.51 ± 0.1	P > 0.05
FBW	3788.89 ± 663.69	4000 ± 734.06	P > 0.05
Apgar Score at 5 min	7.57 ± 1.01	7.55 ± 0.65	P > 0.05
blood thrombi in placenta biopsy	Positive (22)	Negative (58)	P – value

Mean Blood glucose	133.50±28.19	123.18 ± 18.92	P > 0.05
Umbilical PI	1.13 ± 0.29	1.17 ± 0.66	P > 0.05
Mean uterine RI	0.48 ± 0.07	0.49 ± 0.11	P > 0.05
FBW	3808.33 ± 486.23	3956.88 ± 770.33	P > 0.05
Apgar Score at 5 min	7.50± 0.84	7.59 ± 0.80	P > 0.05
interstitial hemorrhoge in placental biopsy	Positive (25)	Negative (55)	P – value
Mean Blood glucose	117 ±17.74	131.35± 21. 8	P > 0.05
Umbilical PI	1.14 ± 0.27	1.17 ± 0.66	P > 0.05
Mean uterine RI	0.46 ± 0.07	0.5 ± 0.11	P > 0.05
FBW	4259.33 ± 940.43	3797.06 ± 581.34	P > 0.05
Apgar score 5 min	7.83± 0.75	7.47 ± 0.8	P > 0.05
fibrinoid necrosis in placental biopsy	Positive (37)	Negative (43)	P – value
Mean Blood glucose	132.59 (±17.59)	123.04 (± 24. 19)	P > 0.05
Umbilical PI	1.31(± 0.81)	1.03 (± 0.16)	P > 0.05
Mean uterine RI	0.46(± 0.09)	0.52 (± 0.11)	P > 0.05
FBW	3637.36 (± 491.98)	4174 ± (779.71)	P <0.05
Apgar Score 5 min	7.37 (±0.92)	7. 75(± 0.62)	P > 0.05
hyalinosis and mural thickening in placental biopsy	Positive (26)	Negative (54)	P – value
Mean Blood glucose	132. 75 (±24.37)	122.8 (± 19.47)	P> 0.05
Umbilical PI	1.10 (±0.26)	1.3 (± 0.7)	P> 0.05
Mean uterine RI	0.98 (± 0.06)	0.49(± 0.12)	P> 0.05
FBW	3792.75 (± 432.96)	3983.33(±813.87)	P> 0.05
Apgar 5 min	7.5 (±0.76)	7.6 (±0.83)	P> 0.05
focal atherosis in placental biopsy	Positive (22)	Negative (58)	P – value
Mean Blood glucose	128. 76 (±30.18)	125.85 (± 18.54)	P> 0.05
Umbilical PI	0.98 (±0.17)	1.22 (± 0.66)	P> 0.05
Mean uterine RI	0.55 (± 0.12)	0.48 (± 0.09)	P> 0.05
FBW	3825 (± 591.4)	3952 (± 748.12)	P> 0.05
Apgar Score at 5 min	7.32 (±0.52)	7.65 (±0.86)	P> 0.05
Intimal thickening in placental biopsy	Positive (26)	Negative (54)	P – value
Mean Blood glucose	130. 88 (±20.86)	123.87 (± 22.22)	P> 0.05
Umbilical PI	1.33 (±0.95)	1.08 (± 0.21)	P> 0.05
Mean uterine RI	0.49 (± 0.14)	0.48(± 0.08)	P> 0.05
FBW	3557.25 (± 479.16)	4112 (±735.14)	P< 0.05
Apgar Score at 5 min	7.24 (±0.71)	7.74(±0.8)	P> 0.05
interstitial oedema in placental biopsy	Positive (32)	Negative (48)	P – value
Mean Blood glucose	132. 72 (±17.57)	122.32 (± 23.59)	P> 0.05
Umbilical PI	1.42 (±0.87)	0.99 (± 0.15)	P> 0.05
Mean uterine RI	0.44 (± 0.1)	0.52(± 0.1)	P> 0.05

FBW	3652 (± 591.61)	4089.29(±729.38)	P> 0.05
Apgar 5 min	7.68 (±1.0)	7.5(±0.65)	P> 0.05

Table (7): *Relation between the histopathologic criteria of placental bed and the placental biopsy other studied parameters in the diabetic group.*

There was high significant difference as regards fetal birth weight and Apgar score at 1 and 5 minutes between both groups of the study (table 8).

		Range	Mean ± SD	T	P
FBW	Control No. (20)	2900-3400	3059.09 ± 325.5	2.637	<0.01
	Diabetic No. (80)	2700-5500	3925.39 ± 462.4		
1 min	Control No. (20)	4-9	6.65 ± 1.5	2.939	<0.01
	Diabetic No. (80)	2-7	4.23 ± 1.42		
5 min	Control No. (20)	8-10	8.54 ± 0.52	3.081	<0.01
	Diabetic No. (80)	6-10	7.56 ± 0.61		

Table (8): *Comparison between the control and diabetic groups as regards fetal birth weight and Apgar Score 1 and 5 minutes.*

Discussion:

Diabetic pregnancy is associated with increased perinatal morbidity and mortality due to congenital malformations, 'unexplained' intra – uterine fetal death and fetal. macrosomia **[12].**

The placenta of the diabetic women has attracted much interest because placental dysfunction is postulated as being partially responsible for the unduly high frequency of perinatal complications **[5].**

This study was carried out on 100 pregnant women of comparable age and parity. They were divided into two groups, the control group comprising 20 normal non-diabetic women and the normotensive diabetic group comprising 80 pregnant diabetic women. There is significant difference between fasting blood sugar in the diabetic and control groups, but there is high significant difference between the two groups regarding 2h -post prandial. Blood sugar and mean blood sugar.

Doppler Study

Umbilical. Artery Doppler

In the present study, the umbilical. Artery pulsatility index (PI) showed no significant difference between the control and the diabetic patients (P> 0.05). The control group had a mean value of 0.98 (± 0.18) while the diabetic group had a mean of 1.16(± 0.58).

In accordance with our results Zimmermann et al. (2014), carried out serial. Measurements of impedance to flow in the umbilical. Artery in 53 women with insulin dependent diabetes and reported that, impedance was within the normal. Range of nondiabetic patients [13].

Uterine artery Doppler:

In the present study, the mean value for the RI in the control group was 0.49 (± 0.08) for the right uterine artery and 0.54 (± 0.12) for the left uterine artery, while that of the diabetic group was 0.48 ((± 0.11) for the right uterine artery and 0.49 (± 0.11) for the left uterine artery. Both groups showed no statistically significant difference between the two means (P> 0.05). The mean uterine artery RI for the control group was 0.51 (± 0.07) and that for the diabetic group was 0.48 (± 0.1) with no statistically significant difference (P > 0.05). Uterine artery flow velocimetry in normotensive diabetic pregnancies does not differ from normal pregnancies.

Mean uterine artery RI did not show significant correlation with the mean blood glucose level (r=0.21). This result indicated that, in the present study, there was no relationship between the uterine artery Doppler and the mean blood glucose in diabetic pregnancies.

Accordingly, the non-diabetic range of uterine artery Doppler waveform analysis was appropriate for normotensive diabetic pregnancies. According to our study, the uterine artery Doppler was not good predictor of adverse fetal outcome in normotensive diabetic pregnancies.

Grunewald et al. (2016) reported that in a study of 24 well controlled IDDM and 25 healthy pregnant women, there was no correlation between glycosylated hemoglobin and random blood sugar and PI values of the umbilical artery, uterine artery and fetal descending aorta. They also concluded that the normal. 3rd trimesters decline in utero-placental and fetal-placental pulsatility indices were absent in the diabetic group. The pulsatility index was not influenced by blood glucose regulation [14].

Middle Cerebral Artery Doppler (Mca)

In the present study, the PI of the control group showed a mean value of 1.85 (± 0.54) while that of the diabetic group was 1.92 (± 0.47) with no significant difference, indicating no evidence of arterial redistribution in normotensive diabetic pregnancy.

The correlation coefficient between the middle cerebral artery PI and the mean blood glucose in the diabetic group was nonsignificant (r = 0.19 and P>0.05) which indicates that blood glucose level has no effect on the middle cerebral artery PI.

Changes in the RI of the cerebral artery appear to be more pronounced than those of the umbilical artery during pregnancy. IUGR, fetal distress, fetal hypertensive disease or toxemia have been associated with elevations in the PI, RI and S/D ratio in the umbilical artery, as well as a decrease in the PI, RI of the cerebral artery **[15].**

In agreement with our results, Ishimatsu et al. (2018), measured impedance to flow in the middle cerebral artery in 43 pregnant women with well- controlled diabetes mellitus at 24-38 weeks of gestation. The PI was within the normal range and was not significantly associated with maternal serum glucose, fructosamine or glycosylated hemoglobin level [**16].**

Leung et al. (2017), found that, Doppler study of the umbilical. Artery pulsatility index and middle cerebral artery pulsatility index was not useful in the prediction of Abnormal pregnancy outcome in GDM [**17**].

Cerebral Umbilical Ratio (Cur)

The cerebral umbilical index, which measures the proportion of flow supplying the brain and the placenta, is now the most powerful parameter for assessment of IUGR and hypoxia first, it takes into account the causes and consequences of the placental insufficiency responsible for IUGR and

hypoxia. Second, it is not heart rate dependent. Third, it has a single cutoff value (CUR is normal. if it is > 1.0), at least during the second half of pregnancy. On the other hand, because IUGR is frequently associated with hypoxia, brain metabolic disturbances, and delayed brain development, the CUR, already an indicator of IUGR, is also and accurate parameter for the prediction of poor perinatal outcome. It is also clear that because the resistance indices are heart rate-dependent it is hazardous to draw any conclusion from a single value of any of these parameters. Only several. Successive daily measures of the Doppler indices can lead to a realistic evaluation of changes in cerebral hemodynamics. Moreover, any significant increase in the umbilical index or decrease in the cerebral or CUR index, even within the range, must be considered pathologic. Conversely, a progressive decrease in the umbilical and cerebral indices with a stable CUR, even outside normal limits, must be considered normal **[18].**

In this study there was no significant difference in the CUR between the diabetic and control groups. Also, there was no correlation between CUR and mean blood glucose level.

None of the control cases had a CUR value < 1.00 while in the diabetic group, one case had a CUR value < 1.00. This case showed a CUR of 0.62 with BPP of 4/8 and adverse fetal outcome. The neonate died 48 hours after an emergency C.S. this case had a normal. MCA PI of 2.27 but an abnormally high umbilical. PI of 3.67 with reversed diastolic blood flow indicating fetal hypoxia.

Others studied 20 healthy women as a control group and 61patients with high-risk pregnancy that had Doppler assessment within two weeks of delivery. A cutoff value of 1.0 was selected to distinguish normal from abnormal C/U ratio values. At this cutoff value, sensitivity was 57.9% specificity was 75.6 % and the proportion of false positive results was 24.4 %. This study supported the well-known correlation between IUGR and abnormal fetal cerebral and umbilical velocimetry (19). This study also found a strong correlation between the C/U ratio and neonatal. Outcome. This study indicates that a normal C/U ratio even when obtained several weeks before delivery is a strong predictor of normal fetal outcome whereas an abnormal result is strongly associated with genetic abnormalities, increased cesarean section rates, perinatal mortality and severe neonatal morbidity, in both SGA and AGA fetuses. It was suggested that evaluation of the high-risk fetus with umbilical. Doppler alone is inadequate and that a better prognostic indicator may be obtained by processing both the umbilical and the cerebral circulations. However, this study is inadequate to determine the clinical usefulness of the C/U ratio (CUR) measurements in evaluation of the fetus at risk for IUGR and neonatal morbidity. Such assessment requires the performance of a randomized clinical trial. [**19]**

Placental Bed

In this study, the placental bed biopsies showed that, in the control group, only 2 cases (10%) showed lack of physiologic changes in the intramyometrial. part of the spiral. arteries while in the diabetic group, 25 cases (31%) showed lack of physiologic changes in the intramyometrial. part of the spiral. arteries, 14 cases (18%) showed blood thrombi, 16 cases (20%) showed interstitial. hemorrhage, 14 cases (18%) showed fibrinoid necrosis, 26 cases (33%) showed hyalinosis and mural. thickening in the intramyometrial. part of the spiral. arteries, 14 cases (18 %) showed focal. atherosis, 15 cases (19%) showed intimal. thickening and 14 cases (18%) showed endarteritis.

In the diabetic group, there were 25 cases with lack of physiologic changes and 55 cases with normal physiologic changes. There was no significant difference in the umbilical artery PI, mean uterine artery RI, mean blood glucose level, CUR, fetal birth weight or Apgar score at 5 min between the two groups.

As regards lack of physiologic changes in the intramyometrial. Portion of the spiral arteries, it was previously reported in cases of hypertension with pregnancy and IUGR rather than in diabetic pregnancy **[20].**

It was found that in this study there was a significant difference in fetal birth weight ($P < 0.05$) between the group I and group III, which indicates that severe placental bed pathological changes are associated with smaller birth weight.

However, there was no significant difference in the mean uterine artery RI, umbilical artery PI or the mean blood glucose level between the 3 subgroups. This does not confirm a relationship between umbilicals. Or uterine Doppler indices and the decidual vascular pathology in normotensive diabetic pregnancies.

Against our results Barth et al. (2017), correlated Doppler indices from the uterine arcuate artery with the decidual vascular histology in patients with type I diabetes and confirmed a relationship between arcute artery Doppler indices and downstream decidual vascular pathology [***10].***

Placental Biopsy

In our study of the placental biopsies showed that, in the control group, 2 cases (10%) showed lack of physiologic changes, 2 cases (10%) showed fibrin thrombi, 1 case (5 %) showed hyalinosis and mural. thickening, 1 case (5%) showed calcification and 2 cases (10%) showed interstitial. oedema. In the diabetic group, 8 cases (10%) showed lack of physiologic changes, 32 cases (40 %) showed fibrin thrombi, 22 cases (27 %) showed blood thrombi, 25 cases (31 %) showed interstitial. hemorrhage, 37 cases (47%) showed fibrinoid necrosis, 26 cases (33%) showed intimal. thickening, 20 cases (25 %) showed calcification, 12 cases (15 %) showed endarteritis, 32 cases (40%) showed interstitial. oedema, and 14 cases (18%) showed thickening of the villous membrane. All these parameters showed statistical significances between the control group and diabetic group except lack of physiologic changes.

Correlating each item of pathological changes in placental biopsy in diabetics separately with mean blood glucose level, umbilical, uterine Doppler indices and Apgar score at 5 minutes. It was found no significant correlation between them.

It was found that there was a significant difference in the fetal. Birth weight in patients showing fibrinoid necrosis and intimal thickening (Table 18) in the placenta compared to those lacking these pathologic findings ($P < 0.05$).

In the present study, the percentage of vascular obliteration in the placental vessels was small, in the form of endarteritis, 12 cases (15%) and infarcts 12 cases (15 %).

In the present study it was also noted that there was a normal villous structure in 72 cases (90%) and only 14 cases (18%) showed thickening of the villous membrane. This might explain the presence of normal uteroplacental (uterine and umbilical), and fetal arterial Doppler indices in this study.

Bracero and associates (2015) studied 25 women with insulin-dependent diabetes in an effort to determine the underlying cause of abnormal umbilical artery Doppler velocimetry. Placental morphology was evaluated and there were no statistically significant differences in placental. Weight, number of tertiary stem villi, number of small muscular arterial. Width, this study suggested that, the cause of abnormal Doppler

results in pregnancies complicated by diabetes is a functional, rather than a structural placental process. [**21**]

Saldeen et al. (2019), studied umbilical artery Doppler, and segments from umbilical and uterine arteries examined histologically and incubated to determine prostacyclin / thromboxane synthesis ratio. They found that placental lesions are associated with lower prostanoid synthesis ratio in diabetes and impaired glucose tolerance compared with normal but not until structural signs of ischemia develop is a rise of umbilical artery blood flow resistance detected. [**5]**

Histological. Examination in 34- AGA and 24- LGA placentae of type I diabetic women and in 22- AGA and 16- LGA placentae of control women revealed several histological abnormalities as presence of nucleated fetal red blood cells, fibrinoid necrosis, villous immaturity that were observed more in diabetic placentae compared with control group. But placentae from LGA- nondiabetic women showed several similarities to those of women with diabetes **[22].**

Adverse Fetal Outcome

In this study there was high significant difference between control and study groups as regards the fetal birth weight, Apgar Score at one and five minutes and stay at incubator.

In this study, we defined adverse fetal outcome as delivery before 37 weeks, Apgar Score at 5 minutes < 7 and / or development of respiratory distress syndrome (RDS) or neonatal hyperglycemia or hypocalcemia Accordingly, the control group cases have no adverse fetal outcome, and only 4 cases of diabetic group had adverse outcome, which was a small number to apply statistical analysis.

The first case was a noninsulin dependent diabetic patient of 5 years duration with fasting blood sugar 110 mg % and a two-hour glucose level of 167 mg % mean blood glucose level was 139 mg % umbilical. Artery PI was 0.80, right uterine artery RI was 0.45, left uterine artery RI was 0.52. The middle cerebral artery PI showed a value of 1.33 and cerebro umbilical ratio was 1.66. Cesarean section was performed at 37 weeks, to deliver a male 4 kg in weight. An Apgar score at 5 minutes was 7. He developed RDS and stay at incubator 7 days. The placenta and placental bed showed focal atherosis and intimal thickening of vessels.

The second case was an insulin dependent diabetic patient of 5 years duration with fasting blood sugar 104 mg% and two hours postprandial glucose level of 184 mg%. Mean blood glucose level was 144 mg% umbilical artery PI was 1.18, right uterine artery RI was 0.54, left uterine artery RI was 0.48. The middle cerebral artery PI showed a value of 2.6 and cerebro umbilical ratio was 2.25. Cesarean section was performed at 37 weeks, to deliver male 4 kg in weight. An Apgar score at 5 minutes was 7 and he developed RDS and stayed at incubator 5 days. The placenta and placental bed showed lack of physiologic changes, elastosis, and mural. Thickening and intimal thickening with thickening of the villous membrane.

The third case was an insulin dependent diabetic patient of 6 years duration with a fasting glucose level 140 mg % and a two-hour glucose level of 200 mg %. The mean blood glucose level was 170 mg % umbilical artery PI was 3.67 with reversal. In the diastolic blood flow waveform. Right uterine artery RI was 0.58, left uterine artery RI was 0.44, the middle cerebral artery PI was 2.27 and cerebro umbilical ratio was 0.62. Emergency Cesarean section was performed at 35 weeks and 4 days for fetal risk delivering a 3250-gm female with 5 minutes Apgar score was 6. The fetus died 48 hours later of RDS. The placenta showed fibrin thrombi, fibrinoid necrosis, intimal thickening, and interstitial oedema while placental bed showed interstitial hemorrhage, intimal thickening, and interstitial oedema.

The fourth case was an insulin dependent diabetic patient of 5 years duration with a fasting glucose level 104 mg % and a two-hour glucose level of 180 mg % mean glucose level was 142 mg. Umbilical artery PI was 1.03, right uterine artery RI was 0.56, left uterine artery RI was 0.62 and mean uterine RI was 0.59 middle cerebral artery PI was 1.69 and cerebro umbilical ratio was 0.61. Cesarean section was performed at 38 weeks and delivered a 4250-gm male with Apgar Score 6 at 5 minutes and stayed at incubator for 10 days for heart failure (which treated). The placenta showed fibrin thrombi and Fibrinoid necrosis while placental bed showed lack of physiological. Changes.

Conclusion:

- The non- diabetic range of uterine artery and MCA Doppler waveform analysis do not differ from that of diabetic pregnancies.
- Abnormal umbilical artery waveform analysis is one of significant predictors of fetal compromise in diabetic pregnancy, but fetal compromise can occur in association with normal Doppler waveform analysis.
- In maternal diabetes the classic redistribution seen in fetal hypoxemia due to uteroplacental insufficiency may not occur in diabetic patient even in severely compromised fetuses.
- In maternal diabetes mellitus, maternal glycemic control has no effect on impedance to flow in the uterine and middle cerebral arteries.
- No relationship was found between the uterine or umbilical arteries Doppler indices and the placental bed decidual vascular pathology in diabetic pregnancies.
- There is high incidence of decidual vascular pathologic changes associated with normotensive diabetic pregnancies.
- There is a poor correlation between the degree of glycemic control and pathological placental changes.
- There was no correlation between placental findings and the Doppler waveform analysis of the umbilical and the uterine arteries.

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